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JENKINS, WILSON, TAYLOR & HUNT, P. A.
3100 TOWER BLVD., Suite 1200
DURHAM, NC 27707

EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
03/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,524	JI ET AL.	
	Examiner	Art Unit	
	SATYANARAYANA R. GUDIBANDE	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☒ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *1-11,13,14,16-18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group XIV (claim 10) drawn to a conjugate for the formula shown in claim 1, wherein TA is alkaloids, and election of species, example 5 disclosed in the specification wherein the TA is camptothecin glycine ester which is an alkaloid in the reply filed on 5/31/07 was acknowledged in the office action dated 8/6/07. The election was made without traverse "with an understanding that under 'election of species' practice, it is understood that upon finding of an allowable species, examination will continue until all species have been examined, or a non-allowable species is found (page 9 of remarks filed on 5/31/07)".

Claim 10 is drawn to the genus of alkaloids was examined in part to the extent it reads on the genus alkaloids. The genus of alkaloids comprises innumerable compounds whose structural characteristics have not been either recited or disclosed in the instant application with the exception of the elected species camptothecin glycine ester. The elected species a conjugate of camptothecin glycine ester was searched and was found to be free of art. The search was extended to the generic formula of claim 1 and was found to be free of art. The search was further extended to the formula shown in claim 7 and was found to be free of art.

Applicant's amendment to claims in the response filed on 12/6/07 has been acknowledged.

Claims 1-18 and 20-22 are pending.

Claim 12 have been withdrawn from further consideration as being drawn to non-elected species, because, cinobufagin is a steroid, clycyrrhetinic acid is an organic acid and scopoletin belongs to a class of coumarins.

Claims 1-11, 13-18 and 20-22 are examined on the merit to the extent that the claims read on the elected species camptothecin glycine ester, which is an alkaloid.

Any objections and rejections made in the office action dated 8/6/07 and not specifically mentioned here are considered withdrawn.

Allowable Subject Matter

Claim 15 is allowable to the extent that it reads on the elected species campothecin which is an alkaloid. The search for prior art has indicated that the other species recited in claim 15 have also been found to be free of prior art.

Withdrawn Rejections

Claim Rejections - 35 USC § 112-New matter

Applicant's arguments, see page 9 and amendments to claim, filed 12/6/07, with respect to claims 1-11, 13, 14 and 16-18 have been fully considered and are persuasive. The rejection of claims 1-11, 13, 14 and 16-18 has been withdrawn under new matter statute.

Claim Rejections - 35 USC § 112-Enablement

Applicant's arguments, see page 14 and 15 and amendments to claim, filed 12/6/07, with respect to claims 1-11, 13 and 14 have been fully considered and are persuasive. The rejection of claims -11, 13 and 14 has been withdrawn under enablement statute.

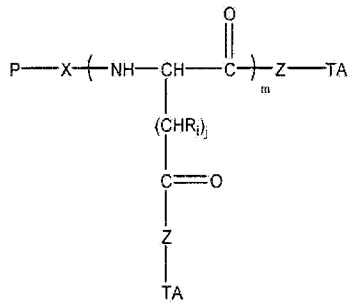
Claim Rejections - 35 USC § 112-2nd paragraph

Applicant's arguments, see 15 and 16, filed 12/6/07, with respect to the rejection(s) of claim(s) 1-11, 13-18 and 20-22 under 35 USC 112-2nd paragraph have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of amendments to claims.

Maintained Rejections

Written Description

Claims 1-11, 13, 14, 16-18 and 20-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as stated in the office action dated 8/6/07 and reiterated below. The rejection has been modified to reflect the amendments to claims made in the response filed on 12/6/07. **Please note that response to applicant's arguments appear at the end of the reiterated rejection.** The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant application, applicants claim a conjugate of hydrophilic polymer-multicarboxyl oligopeptide and drug molecule of the following formula:



wherein,

P is a water soluble polymer; m is an integer from 2-12 inclusive;

j is an integer from 1-6 inclusive;

R_i is a group selected from the group consisting of H, C1-12 alkyl, substituted aryl, aralkyl, heteroalkyl and substituted alkyl;

X is a linking group;

Z is a linking group selected from O and NH; and

TA is a drug molecule.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, "level of skill and knowledge in the

art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated, "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. The MPEP further states that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although, the MPEP does not define what constitute a sufficient number of representatives, the courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant application, claims 1 and 7 recite a limitation, 'P' as a water-soluble polymer. The claim as recited encompass any and all polymer molecules that are water soluble which comprises of myriads of polymer molecules that includes all natural and synthetic polymers. The specification discloses, for e.g., polyethylene glycol, polypropylene, polyvinyl alcohol, polyacrylmorpholine or copolymer thereof, among them, polyethylene glycol and its copolymer are preferable and acidic oligopeptide of amino acid, especially oligopeptide of glutamic acid. The specification only has specific examples related to polyethylene glycol and oligopeptide of glutamic acid (a dimer of the peptide).

The claims 1 and 7 also recite a limitation, 'X' as a linking group wherein the X is not defined adequately neither in the claim as recited nor in the specification. Hence, 'X' as a linking group encompass any and all known and unknown compounds. The specific examples 1-5 (pages 9-13) discloses only $(CH_2)_2OCO$ as the linker. The specification is silent with respect to all the myriads of any and all linking groups as recited in the claims.

The claims 1 and 7 recite a limitation 'TA is a drug molecule' and claim 15 recites the term "PT is a drug molecule". The term "drug molecule" lacks proper definition as recited in the claims and as disclosed in the specification. The specification on page 8, lines 5-13 page 8, provides a broad definition for the drug molecule as "drug molecule including, for example, amino acids, proteins, enzymes, nucleosides, saccharides, organic acids, glycosides, flavonoids, quinones, terpenoids, phenylpropanoid phenols, steroids and glycosides thereof, alkaloids and the like the ingredient of nature medicine used in the treatment of tumor, such as paclitaxel, camptothecin, hydroxylcamptothecin, etoposide and the derivatives thereof". Therefore, the term "drug molecule" as defined includes all natural compounds. Since the definition comprises of

"derivatives thereof", it encompasses all the known and unknown derivatives all the natural compounds. However, the specific examples include only a handful compounds 'paclitaxel, camptothecin, cinobufagin, clycyrrhetinic acid, scopoletin'. Hence the number of specific compounds as in "drug molecules" disclosed does not commensurate with scope of the claims as recited.

Claims 17 and 21 recite a limitation, "another therapeutically active ingredient". The limitation lacks adequate written description in terms of a proper definition as recited in the claims. The specification on page 8, line 24 mentions that the composition may also include other medical agents. Therefore, the claim as recited and specification as disclosed is vastly inadequate in providing a proper definition associated with structural feature for the limitation "another therapeutically active ingredient".

Therefore, the claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to applicant's arguments

Applicants argue that (please see pages 9-14 of remarks filed on 12/6/07) the specification as originally filed meets the written description for the instant invention as claimed. Applicants specifically argue that, the term "water soluble polymer" has sufficient support in the specification on page 3 and 4 of instant specification with a listing of all the different classes of hydrophilic polymers that includes polyethylene glycol (i.e., PEG), polypropylene, polyvinyl alcohol, polyacrylmorpholine or copolymers thereof, copolymers thereof. See Instant

Specification, page 3, lines 20-22. The instant specification also describes a variety of different PEG derivatives by reference to a general structure (see Instant Specification, page 4, lines 22-32), and confirms that other analogs and derivatives of polyethylene glycol, including polypropylene glycol, polyvinyl alcohol, and polyacrylmorpholine and the like are envisioned as being useful in the conjugates of the presently disclosed subject matter. See Instant Specification, page 4, lines 33-35.

Applicants argue that the instant specification describes linking group "X" with the specific structures the following specific structures: $(CH_2)_i$, $(CH_2)OCO$, $(CH_2)_iNHCO$ and $(CH_2)_iCO$, O and NH. See Instant Specification, page 7, lines 18-20. With regards to "drug molecule", applicants argue that the instant specification provides ample description as including a variety of different classes of compounds, such as amino acids, proteins, enzymes, nucleosides, saccharides, organic acids, glycosides, flavonoids, quinones, terpenoids, phenylpropanoid phenols, steroids and glycosides thereof, alkaloids and the like. See Instant Specification, page 8, lines 5-8. Applicants respectfully submit that this listing specifically recites at least thirteen "species" of drug molecules. The instant specification also recites that the drug molecule can be an active ingredient from a plant, specifically reciting the individual molecules cinobufagin (a steroid), clycyrrhetinic acid (an organic acid) and scopoletin (a phenylpropanoid phenol) as being examples of such drugs. See Instant Specification, page 8, lines 9-11. The specification further notes that the drug molecule can be a drug used in the treatment of tumors, specifically reciting paclitaxel (a terpenoid), camptothecin (an alkaloid), hydroxylcamptothecin (an alkaloid), etoposide (a non-alkaloid), and derivatives thereof. See Instant Specification, page 8, lines 11-13. In addition, working Examples 3 and 4 relate to conjugates of the terpenoid paclitaxel. See

Instant Specification, page 10, line 30 to page 11, line 15. Working Example 5 relates to a conjugate of the alkaloid camptothecin glycine ester. See Instant Specification, page 11, line 20 to page 12, line 6. Working Example 6 relates to a conjugate of the steroid cinobufagin. See Instant Specification, page 12, lines 11-20. Working Example 7 relates to a conjugate of the organic acid clycyrrhetinic acid. See Instant Specification, page 12, lines 25-36. Working Example 8 relates to a conjugate of the phenylpropanoid phenol scopoletin. See Instant Specification, page 13, lines 5-15. Additionally, applicants respectfully submit that the instant specification recites that the drugs of the presently disclosed subject matter can comprise functional groups such as amino, carboxyl, and hydroxyl groups and, in vivo, can conjugate to biomolecules including monosaccharide, polysaccharide, nucleoside, polynucleoside and phosphoryl groups. See Instant Specification, page 6, line 30 to page 7, line 3. The instant specification notes that the hydrophilic polymer-multioligopeptide moiety can conjugate to the drug molecules in the same way as the biomolecules do, thereby increasing the drugs physiological half-life and therapeutic duration. See Instant Specification, page 7, lines 4-6.

With regards to the limitation of "another pharmaceutically active ingredient" in claims 17 and 21, applicants respectfully state that one of skill in the art after review of the claims and specification would understand that such recitation refers to the inclusion in the claimed composition of a second medically active agent in addition to drug molecule TA or PT. Applicants respectfully submit that the language "another and "pharmaceutically active" should be sufficient in fulfilling the written description requirement. Further, applicants respectfully submit that it would be understood after review of the instant specification, that the pharmaceutically active agents can include other drug molecules. As noted hereinabove, the term

drug molecule can include a variety of classes of molecule (e.g., amino acids, proteins, enzymes, nucleosides, saccharides, organic acids, glycosides, flavonoids, quinones, terpenoids, phenylpropanoid phenols, steroids and glycosides thereof, alkaloids and the like).

Applicant's arguments filed 12/06/07 have been fully considered but they are not persuasive. Applicants argument that the specification as filed provides ample support to the claims as recited is not persuasive, because, the claim as recited as stated in the office action dated 8/6/07 claims any and all water soluble polymers, any and all linking groups and any and all drug molecules. Mere listing of names of different classes of hydrophilic polymers, structural features of several linking groups, a listing of several classes of molecules as "drug molecules" and mere mention of "another pharmaceutically active ingredient" does not provide adequate support to the claims as recited.

The claim recites "wherein, P is a water soluble polymer". There are innumerable polymers that are water soluble belonging to different classes such as polynucleotides, polypeptides, polysaccharides to name a few apart from the polymers disclosed in the instant specification. If we just look at the number of polymers that can be obtained by a peptide consisting of 50 amino acid residues, we can have 50^{20} polypeptides by only considering naturally occurring amino acid monomers. Therefore, applicant's argument that they have shown support in the specification for the claims as recited with the of applicant's disclosure such as "[h]ydrophilic polymers used in the presently disclosed conjugates **can** include the following: polyethylene glycol (i.e., PEG), polypropylene, polyvinyl alcohol, polyacrylmorpholine or copolymers thereof. See Instant Specification, page 3, lines 20-22" does not provide adequate

support to the specification. As discussed above, the specification does not provide any structural feature of a polypeptide which also belongs to the genus of hydrophilic polymer. the mere mention that "[h]ydrophilic polymers used in the presently disclosed conjugates **can** include the following: polyethylene glycol (i.e., PEG), polypropylene, polyvinyl alcohol, polyacrylmorpholine or copolymers thereof" in the specification fails to provide adequate written description support to the claims as recited. If a limitation is critical to the claim, mere listing of the same in the specification does not provide adequate support the claim as recited. "A claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement" (Please see, 2163 [R-5] Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement). Therefore, the critical limitations from the specification can not be imported into claims but should be recited in the claims for providing proper written description support to the claims.

Claims also recite "a drug molecule". The specification provides a very broad definition the phrase "drug molecule" encompasses. The disclosure lists a variety of different classes of compounds, such as amino acids, proteins, enzymes, nucleosides, saccharides, organic acids, glycosides, flavonoids, quinones, terpenoids, phenylpropanoid phenols, steroids and glycosides thereof, alkaloids and the like. See Instant Specification, page 8, lines 5-8. Applicants respectfully submit that this listing specifically recites at least thirteen "species" of drug molecules. The instant specification also recites that the drug molecule can be an active ingredient from a plant, specifically reciting the individual molecules cinobufagin (a steroid), clycyrrhetinic acid (an organic acid) and scopoletin (a phenylpropanoid phenol) as being

examples of such drugs. See Instant Specification, page 8, lines 9-11. The specification further notes that the drug molecule can be a drug used in the treatment of tumors, specifically reciting paclitaxel (a terpenoid), camptothecin (an alkaloid), hydroxylcamptothecin (an alkaloid), etoposide (a non-alkaloid), and derivatives thereof. See Instant Specification, page 8, lines 11-13. Additionally, applicants respectfully submit that the instant specification recites that the drugs of the presently disclosed subject matter can comprise functional groups such as amino, carboxyl, and hydroxyl groups and, in vivo, can conjugate to biomolecules including monosaccharide, polysaccharide, nucleoside, polynucleoside and phosphoryl groups. As disclosed in the specification, the drug molecule can any of the innumerable compounds that belongs to many genera and classes of compounds. If we take one example such as a protein being a drug in this case, applicants have not shown one drug molecule that belongs to the class of protein with a specific amino acid sequence. Based on the analysis shown above a 50 amino acid polypeptide itself results in millions of peptide compounds. Applicants have not provided any example of peptides with a corresponding amino acid sequence associated with it. Applicants have shown the following drug molecules in their specific examples: working examples 3 and 4 relate to conjugates of the terpenoid paclitaxel. See Instant Specification, page 10, line 30 to page 11, line 15. Working Example 5 relates to a conjugate of the alkaloid camptothecin glycine ester. See Instant Specification, page 11, line 20 to page 12, line 6. Working Example 6 relates to a conjugate of the steroid cinobufagin. See Instant Specification, page 12, lines 11-20. Working Example 7 relates to a conjugate of the organic acid clycyrrhetinic acid. See Instant Specification, page 12, lines 25-36. Working Example 8 relates to a conjugate of the phenylpropanoid phenol scopoletin. See Instant Specification, page 13, lines 5-15.

With respect to "another pharmaceutically active ingredient" applicants argument that the language "another" and "pharmaceutically active" should be sufficient in fulfilling the written description requirement is not persuasive. The words "another" and "pharmaceutically active" does not provide relevant identifying characteristics, i.e., structure or other physical and/or chemical properties to the molecule as required by the written description requirement.

Therefore, the claim(s) 1-11, 13, 14, 16-18 and 20-22 contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 recites the limitation "free hydroxyl" in line 1. There is insufficient antecedent basis for this limitation in the claim. The claim 1 that it depends from does not have an available hydroxyl group in the structure shown in claim 1.

Applicant's amendment to claims 1 and 7 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654